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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,173	12/12/2000	Edward D. Ball	MXI-026DVCN2	5414

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,173	BALL ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in Paper No. 5 is acknowledged. Claims 25-29 are examined on the merits.

Priority

2. This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application. A statement reading "This is a continuation of Application No. 09/151,893, filed 09/11/1998, which is a continuation of 08/451,194, now US Pat No. 5833985, filed on 05/26/1995, which is a divisional of 08/207,344, now abandoned, filed, 03/07/1994." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of the parent nonprovisional application(s) should be included.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. In regards to claim 28, in the recitation of the term *"analogue"*, it is indefinite, because the metes and bounds of this term are not described. Clarification is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth GRP and bombesin and therefore the written description is not commensurate in scope with the claims which read on analogues, wherein analogues encompasses allelic variants, analogues, and fragments of GRP.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of GRP and bombesin, the skilled artisan cannot envision the detailed structure of the encompassed analogues, fragments and or allelic variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus.

At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants, fragments and or analogues are provided in the specification on page 3 lines 18-39 where it is disclosed that "fragments or analogues thereof is intended to include amino acid sequences which differ by one or more amino acid substitutions, additions or deletions from the full length native bombesin and GRP protein, such as allelic variants." However, no disclosure, beyond the mere mention of allelic variants, fragments, or analogues is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only GRP and bombesin molecules meet the written description provision of 35 USC 112, first paragraph.

8. Claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bispecific molecule comprising bombesin and FcγRI, does not reasonably provide enablement for any bispecific molecule comprising a growth factor fr a tumor cell and an antibody or antigen binding fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 25-29 are drawn to a bispecific molecule comprising an autocrine growth factor and an antibody or an antigen binding fragment. Although the specification specification provides and enabling disclosure for a bispecific molecule comprising bombesin and FcγRI, it does not provide to one of skill in the art the necessary steps, procedures, and or components of any other bispecific molecule. Because the specification is silent in this regard, it forces the skilled artisan to experiment.

The factors which must be considered in determining undue experimentation are set forth in *In re Wands* 8 USPQ2d 1400. The factors include: (1) quantity of experimentation, (2) the amount of guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the predictability of the art and, (7) breadth of the claims.

With regards to factors one and two cited above, the quantity of experimentation needed to determine which growth factor receptors are found on tumor cells, the construction of the bispecific molecule, and the analysis of the functionality of the bispecific molecule is high. The specification has only provided to one of skill in the art the procedures and steps for constructing and testing of the bispecific molecule comprising bombesin and FcγRI. The instant specification has not enabled one of skill in the art to make and use any other bispecific molecule, comprising any other components.

With regards to factors four, five and six cited above, it is noted that there is a great deal of unpredictability associated in the treatment of cancer, and in the use of and construction of bispecific molecules. The instant specification fails to provide

details on other bispecific molecules, the components, the process of making, and the effects these other bispecific molecules have on treatment, and their effectiveness in eliciting effector cell response.

With regards to factors three and six cited above, it is noted that the working examples are limited to methods of making and analysis of a bispecific molecule comprising bombesin and FcγRI. Such is not seen as sufficient to support the breadth of the claims, wherein the scope of the claims encompasses bispecific molecules in general. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art ho to use applicant's alleged discovery, not how to find out how to use it for themselves., see *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

Double Patenting

9. Claims 25-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 5,833,985. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the previously issued US Patent No. 5,833,985, are drawn and directed to the same invention. Claims 5-8 of US Patent No. 5,833,985 are drawn to a bispecific molecule, wherein the said bispecific molecule comprises a ligand (bombesin and GRP) and a mAb22 antibody that recognizes FcγRI. Claims 25-29 of the instant application is drawn to a bispecific molecule comprising an autocrine growth factor and an antibody or antigen binding

fragment, wherein the autocrine growth factor is bombesin, GRP, or GRP analogues and the antibody or antigen binding fragment binds to an Fc receptor (FcγRI, FcγRII, or FcγRIII). The prior US Patent No. 5,833,985 differs from the instant application in that the instant application recites generic molecules, wherein the molecule claimed in the prior patent, is a specific example. Therefore the claims of a genus are already anticipated.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 25 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Shin *et al.* Claims 25 and 29 are drawn to a bispecific molecule comprising a growth factor specific for a tumor cell and an antibody or antigen binding fragment which binds the Fc receptor, wherein the Fc receptors are selected from the group consisting of FcγRI, FcγRII, or FcγRIII. Shin *et al.* disclose of a bispecific molecule which comprises a growth factor, IGF1 or IGF2 and a antibody or antigen binding fragment that binds to a Fc receptor, more specifically FcγRI. Furthermore, Shin *et al.* also disclose that IGF aberrant expression leads to autocrine growth of neoplastic cells. Therefore, the claims, of the instant application, are anticipated by Shin *et al.*.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shin *et al.* (J Biol Chem 1994 Feb 18; 269(7):4979-4985) in view of Cuttitta F *et al.* (Nature 1985 Aug 29-Sep 4;316(6031):823-6, see abstract). Claims 25-29 are drawn to a bispecific molecule comprising an autocrine growth factor and an antibody or antigen binding fragment which binds the Fc receptor of an effector cell, wherein said growth factor consists or either bombesin, GRP or GRP analogues, wherein said Fc receptor consists of either FcγRI, FcγRII, or FcγRIII.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Shin *et al.* (see ***Claim Rejections - 35 USC § 102*** for disclosure, *supra*) however fail to disclose of the specific autocrine growth factor bombesin and GRP as part of the bispecific molecule. In addition, Shin *et al.* also fail to disclose of the bispecific molecule

comprising GRP in association with small cell lung carcimoma cell, and how Bombesin or GRP are growth factors that are specific for neoplastic cells or tumor cells.

Cuttitta F *et al.* however do disclose of bombesin and GRP as it relates to small cell lung carcinomas and how these molecules act as autocrin growth factors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conceive of a bispecific molecule comprising an growth factor, bombesin or GRP, and a antibody or antigen binding domain, because the prior art provides sufficient motivation to make and use the invention as claimed. The suggestion/motivation for doing what the applicant has claimed is that it was already known in the prior art the a bispecific molecule comprising a growth factor and a antibody was made and available and that it could be used fo rthe treatment of neoplastic diseases (Shin *et al.*) and that bombesin and GRP are growth factors associated with small cell lung carcinoma (Cuttitta F *et al.*). It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a bispecific molecule comprising a bombesin or GRP and an antibody that binds to Fc receptors, because the art teaches that the bispecific molecule as taught b Shin *et al.* was functional and effective and could be used for treating neoplastic disease. In addition it was also taught in the art that small cell lung carcimona cells express bombesin and GRP and that they acted as growth factors associated with small cell lung carcinoma cells. Therefore it would have been *prima facie* obvious at the time of the invention to switch the growth factor taught by Shin *et al.* with the growth factors

taught in the instant application to derive a bispecific molecule that has the same specificity as the one taught in the instant application.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Christopher Yaen
Art Unit 1642
May 18, 2002